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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/529,713	03/31/2006	Hideyuki Yasuno	18201-003US1 RCJA0213P-US	4470

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EXAMINER	
PANDE, SUCHIRA	

ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
10/29/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

Office Action Summary	Application No.	Applicant(s)	
	10/529,713	YASUNO ET AL.	
	Examiner	Art Unit	
	SUCHIRA PANDE	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *6-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 16-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 March 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/28/05, 3/11/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of group I invention (claims 1-5, and 16-18) in the reply filed on July 15, 2008 is acknowledged. The traversal is on the grounds that Marsh et al. (1999) Genomics vol. 58 (3) pp: 310-312 does not teach the instant amended claims since the amended claims as presented relate to an oligonucleotide consisting of a sequence complementary to a specific region of an allele of a thymidylate synthase promoter and hybridizes to that region under high stringency. Applicants further argue that Marsh et al. does not teach amended claim 1 since the sequence of Marsh et al. comprise additional sequences, in addition to those recited in the claims and does not teach a special technical feature of the claims and therefore it would not be a burden to examine all the claims together. Applicants' arguments were found unpersuasive. First, the lack of unity is based on the broader claim 1, which lacks a special technical feature that binds all the claims together. The amended claim 1, while reciting a closed 'consisting of' language, recites a large sequence, that is (a nucleotide sequence complementary to a strand of a genomic region), which could include other sequences, in addition to the recited portions of a (i) (ii). Further the broader claim 1 does not require a length limitation thus an oligonucleotide of any length that is complementary to a strand of genomic region would anticipate the claim 1. Further, the dependent claim 3 recites that the oligonucleotide of claim 1 comprises SEQ ID No.1, which clearly indicate that the claimed sequence in claim 1 is larger than the SEQ ID No.1 and includes other sequences in addition

to the claimed sequence of SEQ ID No. 1. Thus Marsh et al. does anticipate the broader claim 1 as amended and the claim 1 lacks special technical feature that binds all the claims together. Therefore the product of group I invention does not share the same corresponding special technical feature as the methods recited in the inventions of groups II to V. Since the product of invention I was already known to one of ordinary skill in the art at the time the invention was made, therefore unity of invention is lacking. Burden of search is not a requirement for the lack of unity. Hence the lack of unity is still deemed proper.

2. Claims 6-15 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention. Applicant timely traversed the restriction (election) requirement in the reply filed on July 15, 2008.

Claim Status

3. Applicant amended claims 1-5, 16-18; and added new claims 19-24. Consequently currently claims 1-5, 16-24 are active and will be examined in this action.

Information Disclosure Statement

4. The information disclosure statements (IDS) submitted on 11/28/2005 and 3/11/2008 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Specification

5. The amendments to specification filed on July 15, 2008 are acceptable. The amendment introduces appropriate SEQ ID NOS following the listing of oligonucleotides in the specification on pages 15 and 16 respectively.

Claim Interpretation

6. The claim 1 is written using phrases ---"consists of a nucleotide sequence that is complementary to a strand of a genomic region" --- and ----"at least a portion of"---- this language reads on a sequence of any length consisting of at least a portion of, that is, a fragment of any length of a genomic region consisting at least a portion of the central repeat. Applicant has not defined – "a strand of a genomic region"—so any length of a region of genomic DNA taught by prior art will read upon the instant claims. Prior art cited Marsh et al. teaches sequence that is 100% identical to claimed SEQ ID NO 1, Luo et al. teaches a sequence that is 98% identical to claimed SEQ ID NO 2 (only one mismatch over the entire length). Hence both these sequences will hybridize to the corresponding genomic DNA under both high and low stringency conditions. Hence the hybridization conditions (high and low stringency) recited in the claims do not further limit the claimed product and therefore the cited art applies to the claimed product.

7. Independent claims 1, 16, 20 and 22 are being considered together in claims 1-2, 4 as the claims share common features that are taught by some core references. Aspects of claims that are different are addressed separately.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1-2, 4 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Luo et al. (2002) Biochemical Genetics vol. 40. Nos 1 / 2, pp. 41-51.

Regarding claims 1, Luo et al. teach an isolated oligonucleotide that:

(a) consists of a nucleotide sequence that is complementary to a strand of a genomic region consisting of:

(i) at least a portion of the central repeat unit of three repeat units composing a tandem repeat in the promoter region of a human thymidylate synthase gene (see page 41, abstract and title also see Fig. 4 on page 47, where 3 repeat unit of 28 bp motif in the promoter region of a human thymidylate synthase gene is shown. Luo et al. teach the 28 bp fragment of TSER alleles with 5, 4, 3 and 2 repeat units and additional upstream and downstream sequences flanking these alleles. By teaching three repeat units composing a tandem repeat in the promoter region of a human thymidylate synthase gene, Luo et al. teach at least a portion of the central repeat unit of three repeat units composing a tandem repeat in the promoter region of a human thymidylate synthase gene), and

(ii) at least a portion of the repeat unit located downstream of the central repeat unit; (see title and page 41, abstract also see Fig. 4 on page 47, where sequences upstream and downstream of the central repeat unit are shown); and

(b) hybridizes to the genomic region under highly stringent hybridization conditions. (since Luo et al. teaches the sequence of a promoter region of a human thymidylate synthase gene with the portions of repeats recited in claim 1, that will inherently have absolute complementarity and would hybridize to the genomic region under highly stringent hybridization conditions).

The cited art teaches the sequence of genomic region of human thymidylate synthase gene as specified above will hybridize to the genomic region of human thymidylate synthase gene. The functional language added to the product namely the hybridization conditions are inherent in sequence taught by Luo et al. since it has absolute complementarity to said region.

Regarding claim 2, Luo et al. teach wherein under hybridization conditions that are less stringent than the highly stringent conditions of (b), the oligonucleotide can hybridize either to the genomic region of (a) or instead to a second region, the sequence of which consists of the sequence of at least a portion of the downstream repeat unit of (a)(ii). (see title and page 41, abstract also see Fig. 4 on page 47 where as shown above for claim 1 the cited art teaches oligo of claim 1. The cited art teaches the sequence of genomic region of human thymidylate synthase gene. A fragment of this region specified above will hybridize to the genomic region of human thymidylate synthase gene under highly stringent or less stringent conditions since it has absolute complementarity

with the genomic region. The functional language added to the product namely the hybridization conditions does not add any further structural constraints to the claimed product.

Regarding claims 4, Luo et al. teach an isolated oligonucleotide consisting of a sequence that is complementary to and hybridizes under highly stringent hybridization conditions to either strand of a first genomic region in the promoter region of a human thymidylate synthase gene, the first genomic region being upstream of a second genomic region consisting of:

(i)-at least a portion of the central repeat unit of three repeat units composing a tandem repeat in the promoter region. (see page 41, abstract, also see Fig. 4 on page 47 where as described above for claim 1 sequence of a human thymidylate synthase gene is taught. Luo et al. teach the sequence of Accession no AF279906 promoter region (cited by applicant in the specification) of the human thymidylate synthase where the first genomic region being upstream of a second genomic region consisting of at least a portion of the central repeat unit of three repeat units composing a tandem repeat in the promoter region is taught).

Regarding claim 5 Luo et al. teach the oligonucleotide of claim 4, wherein the nucleotide sequence of the oligonucleotide comprises the nucleotide sequence of SEQ ID NO:2. A search of the nucleic acid database gave following alignment. See the alignment shown below:

SEQ ID NO 2= two tandem repeat 2R of instant specification.

RESULT 3
AF279907

```
LOCUS       AF279907                165 bp    DNA     linear   PRI 14-
OCT-2005
DEFINITION  Homo sapiens thymidylate synthase (TSER) gene, TSER-2
allele,
            partial sequence.
ACCESSION   AF279907
VERSION     AF279907.1  GI:12802219
KEYWORDS    .
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata;
Euteleostomi;
            Mammalia; Eutheria; Euarchontoglires; Primates;
Haplorrhini;
            Catarrhini; Hominidae; Homo.
REFERENCE   1  (bases 1 to 165)
  AUTHORS   Luo,H.R., Lu,X.M., Yao,Y.G., Horie,N., Takeishi,K.,
Jorde,L.B. and
            Zhang,Y.P.
  TITLE     Length polymorphism of thymidylate synthase regulatory
region in
            Chinese populations and evolution of the novel alleles
  JOURNAL   Biochem. Genet. 40 (1-2), 41-51 (2002)
   PUBMED   11989786
REFERENCE   2  (bases 1 to 165)
  AUTHORS   Luo,H.-R., Lu,X.-M., Yao,Y.-G. and Zhang,Y.-P.
  TITLE     Direct Submission
  JOURNAL   Submitted (18-JUN-2000) Laboratory of Cellular and
Molecular
            Evolution, Kunming Institute of Zoology, Chinese Academy of
            Sciences, Jiaochang Donglu 32, Kunming, Yunnan 650223,
China
FEATURES             Location/Qualifiers
     source          1. .165
                     /organism="Homo sapiens"
                     /mol_type="genomic DNA"
                     /db_xref="taxon:9606"
                     /chromosome="18"
                     /map="18p11.32"
     gene            1. .>165
                     /gene="TSER"
                     /allele="TSER-2"
                     /note="thymidylate synthase"
     misc_feature    1. .>165
                     /gene="TSER"
                     /allele="TSER-2"
                     /note="5' flanking region; contains two repeats"
ORIGIN

  Query Match             96.8%;  Score 48.4;  DB 5;  Length 165;
  Best Local Similarity   98.0%;  Pred. No. 7.8e-06;
  Matches   49; Conservative    0;  Mismatches    1;  Indels    0;
Gaps    0;

Qy          1 CGCGGAAGGGGTCCTGCCACCGCGCCACTTGGCCTGCCTCGGTCCCGCCG 50
```

```
                  |||||||||||||||||||||||||||||||||||||||| |||||||||
Db          85 CGCGGAAGGGGTCCTGCCACCGCGCCACTTGGCCTGCCTCCGTCCCGCCG 134
```

Thus claims 1-2 and 4-5 are anticipated by Luo et al.

10. Claims 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by Marsh et al. (1999) Genomics 58 (3) 310-312 (provided to applicant with last action).

Regarding claim 1, Marsh et al. teach an isolated oligonucleotide that:

(a) consists of a nucleotide sequence that is complementary to a strand of a genomic region consisting of:

(i) at least a portion of the central repeat unit of three repeat units composing a tandem repeat in the promoter region of a human thymidylate synthase gene (see page 310, abstract where tandem repeat sequence in human thymidylate synthase enhancer promoter (TSER) is taught. They also teach homozygous triple repeat subjects. Also see page 310 par. 3 where TSER *3 GenBank accession AF127520 is referred to. This sequence teaches three repeat units composing a tandem repeat of a 28 bp sequence in the promoter region of a human thymidylate synthase gene. Hence Marsh et al. teach at least a portion of the central repeat unit of three repeat units composing a tandem repeat in the promoter region of a human thymidylate synthase gene), and

(ii) at least a portion of the repeat unit located downstream of the central repeat unit; and

(b) hybridizes to the genomic region under highly stringent hybridization conditions. (since Marsh et al. teaches the sequence of a promoter region of a

human thymidylate synthase gene with the portions of repeats recited in step a of claim 1, that will inherently have absolute complementarity and would hybridize to the genomic region under highly stringent hybridization conditions).

The cited art teaches the sequence of genomic region of human thymidylate synthase gene as specified above will hybridize to the genomic region of human thymidylate synthase gene. The functional language added to the product namely the hybridization conditions are inherent in sequence taught by Marsh et al. since it has absolute complementarity to said region.

Regarding claim 2, Marsh et al. teach wherein under hybridization conditions that are less stringent than the highly stringent conditions of (b), the oligonucleotide can hybridize either to the genomic region of (a) or instead to a second region, the sequence of which consists of the sequence of at least a portion of the downstream repeat unit of (a)(ii). (as described above for claim 1, see page 310 abstract and par. 3 the cited art teaches oligo of claim 1. The cited art teaches the sequence of genomic region of human thymidylate synthase gene. A fragment of this region specified above will hybridize to the genomic region of human thymidylate synthase gene under highly stringent or less stringent conditions since it has absolute complementarity with the genomic region. The functional language added to the product namely the hybridization conditions does not add any further structural constraints to the claimed product.

Regarding claim 3, Marsh et al. teaches the sequence of SEQ ID no 1. Marsh et al. teach the sequence of the thymidylate synthase enhancer region

(see whole article). A sequence search of database with SEQ ID no 1 gave following match.

See the alignment provided below.

```
  TITLE     Ethnic variation in the thymidylate synthase enhancer
region
            polymorphism among Caucasian and Asian populations
  JOURNAL   Genomics 58 (3), 310-312 (1999)

  Query Match             100.0%;  Score 27;  DB 5;  Length 140;
  Best Local Similarity   100.0%;  Pred. No. 1e+02;
  Matches   27;  Conservative    0;  Mismatches    0;  Indels    0;
Gaps    0;

Qy          1 CTTGGCCTGCCTCCGTCCCGCCGCGCC 27  SEQ ID No.1 Claimed
              |||||||||||||||||||||||||||
Db         66 CTTGGCCTGCCTCCGTCCCGCCGCGCC 92
```

By teaching a sequence that is 100 % identical to the sequence of SEQ ID no 1. Marsh et al. teach wherein the oligonucleotide comprises the nucleotide sequence of SEQ ID NO: 1 (claim 3).

Thus Marsh et al. anticipates claims 1-3.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary.

Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 16 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marsh et al. (1999) Genomics 58 (3) 310-312 in view of Luo et al. (2002) Biochemical Genetics vol. 40. Nos 1 /2 pp. 41-51 and Stratagene 1988 catalog.

Regarding claims 16 and 18, Marsh et al. teach

(A) a first oligonucleotide comprising a nucleotide sequence that is complementary to a strand of a genomic region consisting of:

(i) at least a portion of the central repeat unit of three repeat units composing a tandem repeat in the promoter region); and

(ii) at least a portion of the repeat unit located downstream of the central repeat unit wherein the first oligonucleotide hybridizes to the genomic region under highly stringent hybridization conditions; (teaching of Marsh et al. regarding both steps (i) and (ii) of (A) are described above for claims 1-3)

Regarding claim 18, Marsh et al. teach wherein the first oligonucleotide comprises the nucleotide sequence of SEQ ID NO: 1 or the complement thereof,

```
TITLE     Ethnic variation in the thymidylate synthase enhancer region
            polymorphism among Caucasian and Asian populations
  JOURNAL   Genomics 58 (3), 310-312 (1999)

  Query Match             100.0%;  Score 27;  DB 5;  Length 140;
  Best Local Similarity   100.0%;  Pred. No. 1e+02;
```

```
  Matches   27;  Conservative    0;  Mismatches    0;  Indels    0;
Gaps    0;

Qy          1 CTTGGCCTGCCTCCGTCCCGCCGCGCC 27  SEQ ID No.1 Claimed
              ||||||||||||||||||||||||||||
Db         66 CTTGGCCTGCCTCCGTCCCGCCGCGCC 92
```

and

Regarding claim 16, Luo et al, teach

(B) a second oligonucleotide that hybridizes to a region adiacent to and upstream of the first oligonucleotide under the highly stringent hybridization conditions. (see sections of Luo et al. cited above as applied to claims 1-2, 4-5).

Regarding claim 18, Luo et al, teach the second oligonucleotide comprises the nucleotide sequence of SEQ ID NO: 2 or the complement thereof.

```
  AUTHORS   Luo,H.R., Lu,X.M., Yao,Y.G., Horie,N., Takeishi,K.,
Jorde,L.B. and
            Zhang,Y.P.
  TITLE     Length polymorphism of thymidylate synthase regulatory
region in
            Chinese populations and evolution of the novel alleles
  JOURNAL   Biochem. Genet. 40 (1-2), 41-51 (2002)
   PUBMED   11989786
REFERENCE   2  (bases 1 to 165)
  AUTHORS   Luo,H.-R., Lu,X.-M., Yao,Y.-G. and Zhang,Y.-P.
  TITLE     Direct Submission

ORIGIN

  Query Match             96.8%;  Score 48.4;  DB 5;  Length 165;
  Best Local Similarity   98.0%;  Pred. No. 7.8e-06;
  Matches   49; Conservative    0;  Mismatches    1;  Indels    0;
Gaps    0;

Qy          1 CGCGGAAGGGGTCCTGCCACCGCGCCACTTGGCCTGCCTCGGTCCCGCCG 50
              |||||||||||||||||||||||||||||||||||||| |||||||||
Db         85 CGCGGAAGGGGTCCTGCCACCGCGCCACTTGGCCTGCCTCCGTCCCGCCG 134
```

Regarding claims 16 and 18, neither Luo et al. nor Marsh et al. teach a kit format.

Regarding claims 16 and 18, Stratagene catalog 1988 teaches use of kit format. Stratagene 1988 teaches kits for gene characterization and they also have kit for hybridizing nucleic acids.

It would have been prima facie obvious to one of ordinary skill in the art to package the oligonucleotides taught by Luo et al. and Marsh et al.; for determination of number of polymorphic repeats present in the regulatory portion of thymidylate synthase gene in form of kit as taught by Stratagene, at the time the invention was made. The motivation to do so is provided to one of ordinary skill by Stratagene catalog that states "In actuality, the kit format saves money and resources for everyone by dramatically reducing waste. 2) The other service provided in a kit is quality control.----Stratagene tests all of the components included in each kit in concert, and demonstrates that they perform well together. This can undoubtedly save you weeks of costly and frustrating trouble – shooting."

14. Claims 17 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marsh et al. in view of Luo et al. and Stratagene catalog as applied to claim 16, 18 above further in view of Dobrowolski et al. US PG pub 2004/0219557 A1).

15. Regarding claim 17, Marsh et al. in view of Luo et al. and Stratagene teaches the kit of claim 16.

Regarding claim 19, Marsh et al. teach (a) a first oligonucleotide consisting of the nucleotide sequence of SEQ ID NO:I or the complement thereof;

See alignment below where sequence taught by Marsh et al. comprises the sequence of SEQ ID NO 1.

```
TITLE     Ethnic variation in the thymidylate synthase enhancer region
            polymorphism among Caucasian and Asian populations
  JOURNAL   Genomics 58 (3), 310-312 (1999)

  Query Match             100.0%;  Score 27;  DB 5;  Length 140;
  Best Local Similarity   100.0%;  Pred. No. 1e+02;
  Matches   27;  Conservative    0;  Mismatches    0;  Indels    0;
Gaps    0;

Qy          1 CTTGGCCTGCCTCCGTCCCGCCGCGCC 27  SEQ ID No.1 Claimed
              |||||||||||||||||||||||||||
Db         66 CTTGGCCTGCCTCCGTCCCGCCGCGCC 92
```

And

Regarding claim 19, Luo et al. teach (a) a second oligonucleotide consisting of the nucleotide sequence of SEQ ID NO:2 or the complement thereof;

See alignment below where sequence taught by Luo et al. comprises the sequence of SEQ ID NO 2.

```
  AUTHORS   Luo,H.R., Lu,X.M., Yao,Y.G., Horie,N., Takeishi,K.,
Jorde,L.B. and
            Zhang,Y.P.
  TITLE     Length polymorphism of thymidylate synthase regulatory
region in
            Chinese populations and evolution of the novel alleles
  JOURNAL   Biochem. Genet. 40 (1-2), 41-51 (2002)
   PUBMED   11989786
REFERENCE   2  (bases 1 to 165)
  AUTHORS   Luo,H.-R., Lu,X.-M., Yao,Y.-G. and Zhang,Y.-P.
  TITLE     Direct Submission

ORIGIN

  Query Match             96.8%;  Score 48.4;  DB 5;  Length 165;
  Best Local Similarity   98.0%;  Pred. No. 7.8e-06;
  Matches   49; Conservative    0;  Mismatches    1;  Indels    0;
Gaps    0;

Qy          1 CGCGGAAGGGGTCCTGCCACCGCGCCACTTGGCCTGCCTCGGTCCCGCCG 50
              |||||||||||||||||||||||||||||||||||||| |||||||||
Db         85 CGCGGAAGGGGTCCTGCCACCGCGCCACTTGGCCTGCCTCCGTCCCGCCG 134
```

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to synthesize an oligonucleotide consisting of the sequences recited in SEQ ID NO 1 and SEQ ID NO 2 and package them in the kit format taught by Stratagene based on the teachings of Marsh et al. who teach sequence of a region comprising SEQ ID NO 1 and Luo et al. who teach the sequence of a region comprising SEQ ID NO 2. As noted in *In re Aller*, 105 USPQ 233 at 235, More particularly, where the general conditions of a claim are disclosed in the prior art (Luo et al. and Marsh et al.), it is not inventive to discover the optimum or workable ranges by routine experimentation.' Routine optimization is not considered inventive and no evidence has been presented that the selection of oligonucleotide length or hybridization conditions performed was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

Regarding claim 17, Marsh et al. in view of Luo et al. and Stratagene do not teach the downstream end of the second oligonucleotide is labeled with FITC, and the upstream end of the first oligonucleotide is labeled with the fluorescent dye RED640 or RED705.

Regarding claim 19 neither, Marsh et al. nor Luo et al. teach the oligonucleotide being optionally labeled with a detectable label.

Regarding claim 17, Dobrowolski et al. et al. teaches the downstream end of the second oligonucleotide is labeled with FITC, and the upstream end of the

first oligonucleotide is labeled with the fluorescent dye RED640. (see page 3, par. 0023)

Regarding claim 19, Dobrowolski et al. teach oligonucleotide being optionally labeled with a detectable label (see page 1 par. 0012 where use of labeled detection probe and subsequent detection using FRET is taught, thus Dobrowolski et al. teach oligonucleotide being optionally labeled with a detectable fluorophore label).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the guidelines and principles taught by Dobrowolski et al. to design the oligonucleotide claimed in the instant application as primer/probes to be used for detection of insertion or deletion polymorphisms in the thymidylate synthase regulatory region present in human population as taught to one of ordinary skill by Luo et al. The motivation to do so is provided by Dobrowolski et al. who teach FRET based detection of mutation and state " Air driven thermal cycling is fast, genotyping with fluorescent hybridization probes is simple because it involves no post-PCR manipulation, and melting peak data is easily interpreted. From isolation of DNA to data interpretation, the 5-mutation panel described here is completed in less than 2 hours. Such rapid analysis assures that second tier molecular data is reported along with the primary biochemical data. An additional benefit is that the close tube format simplifies sample tracking and is favorable for avoiding amplicon contamination in the laboratory. Data files from the Light Cycler are easily stored and may be backed up in an off-site archive rendering them safe from loss. This is an

ideal situation for the newborn screening laboratory where large quantities of sensitive clinical data are generated." (see page 5 par. 0032). Based on above teaching one of ordinary skill in the art is motivated to design fluorescent probes as taught by Dobrowolski et al. to *perform FRET based polymorphism detection* using the Light Cycler system with a reasonable expectation of success.

16. Claims 20-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Luo et al. in view of Wittwer et al. US Pat. 6,174,670 B1.

Regarding claims 20-22, Luo et al. teaches all aspects of the claims 20-22 (see details provided above for claims 1-2 and 4 above) except labeling of the oligos at appropriate positions with a fluorescent dye. The cited art teaches the region comprising the claimed isolated oligo.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to synthesize an oligonucleotide consisting of any desired portion of the human thymidylate synthase promoter sequence taught by Luo et al. As noted in *In re Aller*, 105 USPQ 233 at 235, More particularly, where the general conditions of a claim are disclosed in the prior art (Luo et al.), it is not inventive to discover the optimum or workable ranges by routine experimentation.' Routine optimization is not considered inventive and no evidence has been presented that the selection of oligonucleotide length or hybridization conditions performed was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

Regarding claims 20-22, Wittwer et al. teaches labeling of the oligos at appropriate positions with a fluorescent dye.

Regarding claim 20, Wittwer et al. teaches wherein the upstream end of the oligonucleotide is labeled with a fluorescent dye (see Fig. 18 where schematic shows how FRET based detection is performed. Here the upstream end of the oligonucleotide is labeled with a fluorescent dye).

Regarding claim 21, Wittwer et al. teaches wherein the nucleotide sequence of the oligonucleotide consists of the sequence complementary to the genomic region (see Fig. 18 top part of panel where adjacent hybridization probes are shown).

Regarding claim 22, Wittwer et al. teaches wherein the downstream end of the oligonucleotide is labeled with a fluorescent dye (see fig. 18 where the downstream end of the oligonucleotide 3' end is shown labeled with a fluorescent dye F).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the guidelines and principles taught by Wittwer et al. to design the oligonucleotide claimed in the instant application as primer/probes to be used for detection of insertion or deletion polymorphisms in the thymidylate synthase regulatory region present in human population as taught to one of ordinary skill by Luo et al. The motivation to do so is provided by Wittwer et al. who teach FRET based detection of mutation and state "It will be appreciated that the particular probes and primers disclosed herein for detection of the factor V Leiden mutation" are merely illustrative, and that a person of

ordinary skill in the art will be able to design other probes and primers for detection of mutation without undue experimentation by following the principles and guidelines set forth herein. It should also be recognized that although the invention is described with respect to detection of a single base mutation in genomic DNA, the same principles can be applied to detection of a mutation in cDNA.-----Further, the same technique can be used to detect insertions and deletions be designing the hybridization probe so that it melting temperature changes when the mutation or polymorphism is present. The invention can be used to detect any known mutation where a probe can be designed to differ in melting temperature when hybridized to mutant vs. wild type" (see col. 45 lines 48-67). The sequence of human thymidylate synthase gene upstream regulatory region containing the central repeat and its upstream or downstream flanking region were known to one of ordinary skill at the time of the invention. So using the guidance provided by Wittwer et al. one of ordinary skill in the art would be able to design probes to perform FRET based polymorphism detection to determine the no of repeats present in regulatory region of human thymidylate synthase a given human population.

17. Claims 23 is rejected under 35 U.S.C. 103(a) as being unpatentable over Marsh et al. (1999) Genomics 58 (3) 310-312; in view of Dobrowolski et al. US PG pub 2004/0219557 A1 .

Regarding claim 23, Marsh et al teaches the sequence of a region comprising the sequence of SEQ ID NO: 1.

A sequence search of database with SEQ ID no 1 gave following match.

See the alignment provided below.

```
  TITLE     Ethnic variation in the thymidylate synthase enhancer
region
            polymorphism among Caucasian and Asian populations
  JOURNAL   Genomics 58 (3), 310-312 (1999)

  Query Match             100.0%;  Score 27;  DB 5;  Length 140;
  Best Local Similarity   100.0%;  Pred. No. 1e+02;
  Matches   27;  Conservative    0;  Mismatches    0;  Indels    0;
Gaps    0;

Qy          1 CTTGGCCTGCCTCCGTCCCGCCGCGCC 27  SEQ ID No.1 Claimed
              |||||||||||||||||||||||||||
Db         66 CTTGGCCTGCCTCCGTCCCGCCGCGCC 92
```

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to synthesize or make an oligonucleotide consisting of SEQ ID NO.1 from the human thymidylate synthase promoter sequence taught by Marsh et al. As noted in *In re Aller*, 105 USPQ 233 at 235, More particularly, where the general conditions of a claim are disclosed in the prior art (Marsh et al.), it is not inventive to discover the optimum or workable ranges by routine experimentation.' Routine optimization is not considered inventive and no evidence has been presented that the selection of oligonucleotide length or hybridization conditions performed was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art. Thus cited art teaches an oligonucleotide consisting of SEQ ID NO: 1. The oligo taught by cited art is unlabeled.

Regarding claims 23 Marsh et al. do not teach an oligo that is optionally labeled with a detectable label.

Regarding claims 23, Dobrowolski et al. teaches labeling an oligo with fluorescent label (see page 3 par. 0023 where FITC and LCred640 labeled oligos are taught)

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the fluorescent labels taught by Dobrowolski et al. to design the oligonucleotide claimed in the instant application as primer/probes to be used for detection of insertion or deletion polymorphisms in the thymidylate syntheses regulatory region present in human population as taught to one of ordinary skill by Lou et al. The motivation to do so is provided by Dobrowolski et al. who teach FRET based detection of mutation and state "Air driven thermal cycling is fast, genotyping with fluorescent hybridization probes is simple because it involves no post-PCR manipulation, and melting peak data is easily interpreted. From isolation of DNA to data interpretation, the 5-mutation panel described here is completed in less than 2 hours. Such rapid analysis assures that second tier molecular data is reported along with the primary biochemical data. An additional benefit is that the close tube format simplifies sample tracking and is favorable for avoiding amplicon contamination in the laboratory. Data files from the Light Cycler are easily stored and may be backed up in an off-site archive rendering them safe from loss. This is an ideal situation for the newborn screening laboratory where large quantities of sensitive clinical data are generated." (see page 5 par. 0032). Based on above teaching one of ordinary skill in the art is motivated to design fluorescent probes using the fluorophores taught by Dobrowolski et al. to *perform FRET based*

polymorphism detection using the Light Cycler system with a reasonable expectation of success.

18. Claims 24 is rejected under 35 U.S.C. 103(a) as being unpatentable over Luo et al. (2002) Biochemical Genetics vol. 40. Nos 1 /2 pp. 41-51; in view of Dobrowolski et al. US PG pub 2004/0219557 A1.

Regarding claim 24, Luo et al teaches the sequence of a region comprising the sequence of SEQ ID NO: 2.

A search of the nucleic acid database gave following alignment. See the alignment shown below:

SEQ ID NO 2= two tandem repeat 2R of instant specification.

```
RESULT 3
AF279907
LOCUS       AF279907                 165 bp    DNA     linear   PRI 14-
OCT-2005
DEFINITION  Homo sapiens thymidylate synthase (TSER) gene, TSER-2
allele,
            partial sequence.
ACCESSION   AF279907
VERSION     AF279907.1  GI:12802219
REFERENCE   1  (bases 1 to 165)
  AUTHORS   Luo,H.R., Lu,X.M., Yao,Y.G., Horie,N., Takeishi,K.,
Jorde,L.B. and
            Zhang,Y.P.
  TITLE     Length polymorphism of thymidylate synthase regulatory
region in
            Chinese populations and evolution of the novel alleles
  JOURNAL   Biochem. Genet. 40 (1-2), 41-51 (2002)
   PUBMED   11989786
REFERENCE   2  (bases 1 to 165)
  AUTHORS   Luo,H.-R., Lu,X.-M., Yao,Y.-G. and Zhang,Y.-P.
  TITLE     Direct Submission
  JOURNAL   Submitted (18-JUN-2000) Laboratory of Cellular and
Molecular
            Evolution, Kunming Institute of Zoology, Chinese Academy of
            Sciences, Jiaochang Donglu 32, Kunming, Yunnan 650223,
China
ORIGIN

  Query Match             96.8%;  Score 48.4;  DB 5;  Length 165;
```

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  Best Local Similarity   98.0%;  Pred. No. 7.8e-06;
  Matches   49; Conservative    0;  Mismatches    1;  Indels    0;
Gaps    0;

Qy           1 CGCGGAAGGGGTCCTGCCACCGCGCCACTTGGCCTGCCTCGGTCCCGCCG 50
               ||||||||||||||||||||||||||||||||||||||| |||||||||
Db          85 CGCGGAAGGGGTCCTGCCACCGCGCCACTTGGCCTGCCTCCGTCCCGCCG 134
```

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to synthesize or make an oligonucleotide consisting of SEQ ID NO.2 from the human thymidylate synthase promoter sequence taught by Luo et al. As noted in *In re Aller*, 105 USPQ 233 at 235, More particularly, where the general conditions of a claim are disclosed in the prior art (Luo et al.), it is not inventive to discover the optimum or workable ranges by routine experimentation.' Routine optimization is not considered inventive and no evidence has been presented that the selection of oligonucleotide length or hybridization conditions performed was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art. Thus cited art teaches an oligonucleotide consisting of SEQ ID NO:2. The oligo taught by cited art is unlabeled.

Regarding claims 24 Luo et al. do not teach an oligo that is optionally labeled with a detectable label.

Regarding claims 24, Dobrowolski et al. teaches labeling an oligo with fluorescent label (see page 3 par. 0023 where FITC and LCred640 labeled oligos are taught)

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the fluorescent labels taught by Dobrowolski et al. to design the oligonucleotide claimed in the instant application as primer/probes to be used for detection of insertion or deletion polymorphisms in the thymidylate synthase regulatory region present in human population as taught to one of ordinary skill by Luo et al. The motivation to do so is provided by Dobrowolski et al. who teach FRET based detection of mutation and state "Air driven thermal cycling is fast, genotyping with fluorescent hybridization probes is simple because it involves no post-PCR manipulation, and melting peak data is easily interpreted. From isolation of DNA to data interpretation, the 5-mutation panel described here is completed in less than 2 hours. Such rapid analysis assures that second tier molecular data is reported along with the primary biochemical data. An additional benefit is that the close tube format simplifies sample tracking and is favorable for avoiding amplicon contamination in the laboratory. Data files from the Light Cycler are easily stored and may be backed up in an off-site archive rendering them safe from loss. This is an ideal situation for the newborn screening laboratory where large quantities of sensitive clinical data are generated." (see page 5 par. 0032). Based on above teaching one of ordinary skill in the art is motivated to design fluorescent probes using the fluorophores taught by Dobrowolski et al. to *perform FRET based polymorphism detection* using the Light Cycler system with a reasonable expectation of success.

Conclusion

19. All claims under consideration 1-5, and 16-24 are rejected over cited prior art.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to SUCHIRA PANDE whose telephone number is (571)272-9052. The examiner can normally be reached on 8:30 am -5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Suchira Pande
Examiner

Art Unit 1637

/Suryaprabha Chunduru/
Primary Examiner, Art Unit 1637